UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/876,252	06/07/2001	Dominic P. Behan	AREN-0240	8181

35133 7590 10/05/2004

COZEN O'CONNOR, P.C.
1900 MARKET STREET
PHILADELPHIA, PA 19103-3508

EXAMINER	
BASI, NIRMAL SINGH	

ART UNIT	PAPER NUMBER
1646	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action	Application No.	Applicant(s)	
	09/876,252	BEHAN ET AL.	
	Examiner	Art Unit	
	Nirmal S. Basi	1646	

--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 13 September 2004 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

a) ☒ The period for reply expires 3 months from the mailing date of the final rejection.

b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.

2. ☐ The proposed amendment(s) will not be entered because:

   (a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);

   (b) ☐ they raise the issue of new matter (see Note below);

   (c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or

   (d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

   NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.

4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).

5. ☒ The a)☐ affidavit, b)☐ exhibit, or c)☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: *See Continuation Sheet*.

6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.

7. ☒ For purposes of Appeal, the proposed amendment(s) a)☐ will not be entered or b)☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

   The status of the claim(s) is (or will be) as follows:

   Claim(s) allowed: _____.

   Claim(s) objected to: _____.

   Claim(s) rejected: *101-132*.

   Claim(s) withdrawn from consideration: *133-144*.

8. ☐ The drawing correction filed on _____ is a)☐ approved or b)☐ disapproved by the Examiner.

9. ☑ Note the attached Information Disclosure Statement(s)(PTO-1449) Paper No(s). 9/22/04

10. ☐ Other: _____

BRENDA BRUMBACK
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Continuation of 5. does NOT place the application in condition for allowance because: applicants arguments do not overcome the rejection under35 USC101 and 35 USC 1st paragraph, of record in the Office Action mailed 7/12/04. Claims 101-132 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility. Applicant argues:

a) The functionality of the non-endogenous constitutively activated version of GPR38 (V297K) is shared with that of the endogenous receptor (GPR38) and the skilled artisan would readily and immediately equate the functionalities of GPR38 with GPR38 (V297K),

b) A well established utility exists for GPR38 and, thus, for GPR38 (V297K). GPR38 (V297K) differs from GPR38 by a single amino acid and yields a constitutively active version of the endogenous receptor.

c) GPR38, which is expressed in the thyroid, has a well-established utility for the prevention of exacerbation of or treatment of Graves's disease. Activation of GPR38 leads to increase in intracellular camp. Activation of TSH leads to an increase in intracellular cAMP. It follows that an agent that inhibits a thyroid pathway leading to an increase in intracellular camp would have a well established utility for the prevention of exacerbation of or treatment of Graves disease.

d) GPR38 (V297K) has a specific and substantial utility in that inverse antagonism of GPR38 (V297K) and by implication, GPR38, is useful in preventing or treating Graves's disease.

Applicant's arguments have been fully considered but not found persuasive. Examiner is not disputing that GPR38 and GPR38 (V297K) may both be G protein coupled receptors. Based on the record, there is not a "well established utility" for the claimed invention, GPR38 (V297K) or its related receptor GPR38. Applicant has asserted utilities for the specifically claimed invention of claims 101-132. Provisional application No. 60/123,945, pages 7, specifically states, that GPR38 is an orphan receptor, and "Gaining an understanding of the normal physiological role of [GPR38] will initially involve...identification of [its] endogenous ligand(s). Further, Provisional application No. 60/123,945, pages 7 and 8, specifically states, disclosed is that, "GPR38 has been reported to be closely related to the type 1 neurotensin receptor-1 and growth hormone secretarogue receptor of the GPCR, and is reportedly expressed in thyroid gland, stomach and bone marrow". Therefore, GPR38 is an orphan receptor for which the normal physiological role is unknown, and the endogenous ligand specific for that receptor has not been identified or is not know. As disclosed in the specification, GPCRs bind to a G protein (e.g. Gq, Gs, Gi, Gz, Go) and effect second messenger signaling which results in cellular activation or cellular inhibition. Gs stimulates the enzyme adnenylyl cyclase, Gi (Gz and Go) inhibit this enzyme. Adenylyl cyclase catalyses the conversion of ATP to cAMP. The inhibition or stimulation of adenylyl cyclase affects cAMP levels in the cell. Cyclic AMP, in turn, drives gene expression by promoting the binding of a camp-responsive DNA binding protein or transcription factor that binds to the promoter at specific sites and drives expression of specific genes. There are many genes and proteins that are directly or indirectly regulated by changes in cAMP levels. On the other hand Gq and Go are associated with activation of enzyme phospholipase C, which hydrolyses PIP2, releasing intracellular messengers DAG and IP3. It is well established in the art that although GPCRs share the same common structural motif, they interact with specific G proteins and have divergent effects. The G protein that interacts with GPR38 is not known or disclosed. The effect of activating or inhibiting GPR38 is not known. The ligand for GPR38 is not known. The physiological function of GPR38 is not know. All GPCRs are not involved in the same disease state or dysfunction. For example, Exibit A, discloses TSH receptor is a member of the family of G protein coupled receptors and is structurally similar to the receptors for lutenizing hormone and follicle stimulating hormone (page 1390, column 2, fourth paragraph). These receptors share significant amino acid sequences and have large extracellular domains, are involved in hormone binding but have different effects. TSH binds to its receptor, adenylyl cyclase is stimulated and cAMP levels in the cells increase. TSH also causes activation of phospholipase C, hydrolysis of phosphphatidylinositols, increases cytoplasmic Ca2+ and activates protein kinase C (Exibit A, column 2, last paragraph). There is no disclosure in the specification or prior art that discloses that GPR38 (V297K) or GPR38 is useful in preventing or treating Graves's disease. Although, Applicants argues Graves disease was characterized by IgG antibodies that bound to and activated the TSH receptor (a GPCR) and activation of TSH leads to an increase in intracellular cAMP it does not follow that an agent that inhibits a thyroid pathway leading to an increase in intracellular cAMP would have a well established utility for the prevention of exacerbation of or treatment of Graves disease. Agonists and antagonits to GPR38 (V297K) have not been shown to have any effect on IgG antibodies that bind and activate TSH receptor. No agonists and antagonists that effect GPR38 are disclosed. GPR38 or its related receptors, type 1 neurotensin receptor-1 and growth hormone secretarogue receptor, have not been disclosed to be involved in Graves disease dysfunction. There is no disclosure that changing cAMP levels in a cell by modulating GPR38 (V297K) or GPR38 would have any effect on Graves's disease. It not even known if GR38 actually increases cAMP levels upon binding ligand. The is no disclosure of what specific effect inverse antagonism of GPR38 (V297K) and by implication, GPR38, would have on Graves disease. Further, the utility of using GPR38 (V297K) to prevent or treat Grave's disease is not disclosed in the specification. The agonists and antagonists that bind to the mutated receptor maynot have the same effect on the native receptor. The relationship of TSH receptor, GPR38, cAMP levels and Grave's disease, relied on by applicant to argue utility, were not disclosed in instant application. Therefore, using GPR38 to prevent or treat Grave's disease cannot be used to support utility in instant application.

Therefore, the specification discloses general functional activities of G-protein coupled receptors (GPCR) which may be applicable to G-protein coupled receptors but does not disclose any activity associated with the specific GPR38 (V297K), of instant invention. As disclosed in the prior Office Action, the superfamily of G-protein-coupled receptors are highly divergent in their effects and include receptors for hormones, neurotransmitters, paracrine substances, inflammatory mediators, certain proteinases, taste and odorant molecules, and even photons and calcium ions. The GPR38 (V297K), of instant invention is considered by the examiner to be a member of the orphan receptor of G-protein coupled receptors i.e. seven transmembrane receptor with no known endogenous ligands. Further, a position that the GPR38 (V279K), is related, through homology, to known orphan receptors may be true, but the art shows it requires more than the disclosed homology to assign a function to an orphan receptor, knowledge of the endogenous ligand for the receptor is required.

The utilities asserted by Applicant are not specific or substantial. Since no specific function of the polypeptide of instant invention is known, and the hypothesized function is based entirely on conjecture from homologous polypeptides, the asserted utilities are not specific to instant polypeptide, but rather are based on family attributes. Neither the specification nor the art of record disclose the GPR38 (V297K), fragments or variants thereof useful to identify drugs that affect said protein and modulate its activity. Similarly, neither the specification nor the art of record disclose any instances where disorders can be effected by interfering with the activity using the GPR38 (V297K), or related GPR38, or using fragments or variants thereof. Thus the corresponding asserted utilities are essentially methods of using GPR38 (V297K), to identify disease states associated with 2GPR38 (V297K), dysfunction and as targets for drug discovery.

Therefore the asserted utilities are essentially methods of testing for or for potentially treating unspecified, undisclosed diseases or conditions, which does not define a "real world" context of use. Treating or testing for compounds that interact with GPR38 (V297K), which may be implicated in an unspecified, undisclosed disease or condition would require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use. Since neither the specification nor the art of record disclose any activities or properties that would constitute a a real world context of use for the claimed GPR38 (V297K), further experimentation is necessary to attribute a utility to the claimed polypeptides and fragments thereof. See Brenner v. Manson, 383 U.S. 519, 535B36, 148 USPQ 689, 696 (1966) (noting that Congress intended that no patent be granted on a chemical compound whose sole utility consists of its potential role as an object of use testing, and stated, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion.").

Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the claimed GPR38 (V297K), further experimentation is necessary to attribute a utility to the claimed GPR38 (V297K). The instant application does not disclose the biological role of GPR38 (V297K), or its significance. The utilities are not considered to be specific and substantial because the specification fails to disclose any particular function or biological significance for the GPR38 (V297K), of the instant invention. The disclosed protein, whose cDNA has been isolated, is said to have a potential function based upon its amino acid sequence similarity to other known proteins. After further research, a specific and substantial credible utility might be found for the claimed isolated compositions. This further characterization, however, is part of the act of invention and until it has been undertaken, Applicants claimed invention is incomplete.

Further, the rejection is based on the failure to disclose sufficient properties of the protein and/or polynucleotide to support an inference of utility. GPR38 (V279K), belongs is a family in which the members have divergent functions. Assignment to this family does not support an inference of utility because the members are not known to share a common utility. There are some protein families for which assignment of a new protein in that family would convey a specific, substantial and credible utility to that protein. For example, some families of enzymes such as proteases, ligases, telomerases, etc. share activities due to the particular specific biochemical characteristics of the members of the protein family such as non-specific substrate requirements, that are reasonably imputed to isolated compositions of any member of the family.

The diversity of the biochemical function and the wide range of regulatory pathways involving GTP-binding proteins is well known in the art. Without some common biological activity for the family members, a new member would not have a specific, substantial, or credible utility when relying only on the fact that it has structural similarity to the other family members. The members of the family have different biological activities which may be related to tissue distribution but there is no evidence that the claimed compounds share any one of diverse number of activities. That is, no activity is known to be common to all members. To argue that all the members can be used for toxicology testing, diagnosis is to argue a general, nonspecific utility that would apply to virtually every member of the family, contrary to the evidence. Further, any compound could be considered as a regulator or modulator of tissue in that any compound, if administered in the proper amount, will stimulate or inhibit tissue. For example, salt, ethanol, and water are all compounds which will kill cells if administered in a great enough amount, and which would stimulate cells from which these compounds had been withheld, therefore, they could be considered regulators or modulators of tissue. However, use of these compounds for the modulation of tissue would not be considered a specific and substantial utility unless there was some disclosure of, for example, a specific and particular combination of compound/composition and application of such in some particular environment of use. Further, the specification does not disclose the significance of any test results, nor is there any evidence that the significance was known as of the filing date. If the expression of the claimed GPR38 (V297K), increases, is this a positive or negative outcome? Would this be a toxic response or not? The disclosure is insufficient to evaluate the results of the test in any meaningful manner.

Without knowing a biological significance of the claimed polypeptides, one of ordinary skill in the art would not know how to use the claimed invention in its currently available form in a real world manner based on the diversity of biological activities possessed by GTP-binding proteins. Contrast Brenner, 148 USPQ at 694 (despite similarity with adjacent homologue, there was insufficient likelihood that the steroid would have similar tumor-inhibiting characteristics), with In re Folkers, 145 USPQ 390, 393 (CCPA 1965) (some uses can be immediately inferred from a recital of certain properties) or In re Brana, 34 USPQ 1436, 1441 (Fed. Cir. 1995) (evidence of success in structurally similar compounds is relevant in determining whether one skilled in the art would believe an asserted utility; here, an implicit assertion of a tumor target was sufficiently specific to satisfy the threshold utility requirement).

The implication that the claimed invention has utility in testing, drug development and disease diagnosis/treatment, do not meet the standards for a specific, substantial, and or well-established utility for reasons set forth above.

In all cases a practical utility of an invention may be derived from belonging to a broad class of inventions. The requirement in any particular case, however, is that practical utility can be inferred if each and every member of the broad class possesses a common utility. The question in the instant application is whether the members of the family of proteins to which the claimed invention is structurally related have, individually, a specific, substantial and credible or well-established utility. Applicant has failed to show by a preponderance of the evidence, in enough detail, with respect to the described GPR38 (V297K), has any substantial use. The record shows that the GTP-binding protein family is diverse, and has such a broad definition, that a common utilitycannot be defined. Moreover, the evidence of record is inadequate to determine the disease(s), drug(s) or toxicological screen(s) for which the compounds would be useful. In Brenner, the Court approved a rejection for failure to disclose any utility for a compound where the compound was undergoing screening for possible tumor-inhibiting effects and an adjacent homologue of the compound had proven effective. Brenner, 148 USPQ at 690. Here, there is no evidence that the claimed isolated compounds have any utility.

7. Claims 101-132 remain rejected under 35 U.S.C. 112, first paragraph, for reasons set forth in the previous Office Action. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. Since neither the specification nor the art of record disclose any activities or properties that would constitute a real world context of use for the claimed cDNA encoding GPR38 (V297K), further experimentation is necessary to attribute a utility to the claimed polynucleotide.